Hypoalbuminemia as a marker of adverse outcome in children admitted to pediatric intensive care unit

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Received - 12 September 2017 Initial Review - 20 October 2017 Published Online - 02 December 2017

ABSTRACT

Background: Research on critically ill adult patients has shown the usefulness of albumin as a predictor of increased morbidity and mortality. There is a paucity of similar data in pediatric age group. **Objective:** The objective of the study was to know the incidence of hypoalbuminemia in children admitted to pediatric intensive care unit (PICU) and its correlation to disease severity and clinical outcome. **Materials and Methods:** This was a prospective observational study conducted at the PICU of a tertiary care hospital. Children of age group 1 month – 18 years admitted to the PICU were included in the study. Serum albumin levels were estimated at the time of admission to PICU. Pediatric index of mortality 2 (PIM2) scoring system was used to assess the severity of illness at admission and to calculate the predicted death rate (PDR). The independent sample t-test and Fisher's exact test were used to compare the albumin levels with PDR and duration of hospital or PICU stay. Mortality risk was computed using Pearson's Chi-square test. Multivariate regression analysis was performed to evaluate whether hypoalbuminemia is an independent predictor of mortality. **Results:** Mean serum albumin level in this study was 3.38±0.89 g/dL. The incidence of hypoalbuminemia was 44.1%. The PDR (calculated using PIM2 score) was increased in children with hypoalbuminemia compared with the normal albumin level group (p=0.004). As compared to children with normal albumin levels, children with hypoalbuminemia had longer duration of PICU stay (95% confidence interval (CI) for difference 0.86–3.03; p=0.05), higher need for ventilator support (odds ratio (OR) 4.2, p=0.003) and higher mortality (OR 0.16, p=0.002). The association of serum albumin levels with mortality remained significant even after adjusting for age and PDR by PIM2 score (OR=3.68; 95% CI, 1.76–7.74; p<0.001). **Conclusion:** Hypoalbuminemia is a significant predictor of mortality and morbidity in critically ill children.

Key words: *Critically Ill, Mechanical ventilation, Pediatric index of mortality 2 score, Serum albumin*

Albumin is synthesized in liver and forms about 60–70% of the total plasma proteins. It contributes to 80% of the colloidal osmotic pressure and thus, it plays a key role in the regulation of blood volume [1]. It is also involved in the binding and transport of various molecules including bilirubin, bile salts, hormones, micronutrients, and some drugs [2]. About two-thirds of albumin resides mainly in the extravascular space. Hypoalbuminemia is commonly attributed to either decreased synthesis (malnutrition and chronic liver disease) or increased loss (nephropathy and protein-losing enteropathy). Albumin is also considered as a negative acute phase reactant, and hypoalbuminemia is known to occur in infection and injury. Hypoalbuminemia is a common finding in the critically ill patients. Critical illness alters the rates of synthesis and degradation of albumin as well as its distribution between the intravascular and extravascular compartments. Altered distribution in critical illness is related to an increase in capillary permeability [3]. Research on critically ill adult patients has shown the usefulness of albumin as a predictor of increased morbidity and mortality. Hypoalbuminemia is associated with poor outcomes in adult critical illness [4-7]. However, there is a paucity of data on the incidence and significance of hypoalbuminemia in critically ill children, and only limited studies are available [8-12]. This study was conducted to evaluate hypoalbuminemia as a marker of adverse outcome in critically ill children.

MATERIALS AND METHODS

This was a prospective, single-center study conducted at the pediatric intensive care unit (PICU) of a tertiary care hospital over a period of 8 months from January 2012 to August 2012. The study protocol was approved by the Institutional Ethics Committee. A written informed consent was obtained from the parents before inclusion in the study. Subjects of the study were children from 1 month to 18 years of age admitted to PICU. Admission to PICU was based on the decision of the treating consultant. Exclusion criteria included those subjects in whom hypoalbuminemia were expected to be attributable to a pre-existing condition. These included subjects who are malnourished, i.e., weight and/or height <3rd centile (2007 WHO reference),

those with chronic disease affecting the gastrointestinal system or liver or kidney (protein losing enteropathy, chronic liver disease, nephrotic syndrome, and end-stage renal disease). Children with thermal burns and those who received fresh frozen plasma or whole blood or albumin within 4 weeks before admission in PICU were also excluded. Serum albumin level done within first 48 h of admission was considered as admission albumin level. Estimation of albumin was done by dye binding method with bromocresol green [13]. Hypoalbuminemia was defined as serum albumin level <2.5 g/dl for children aged <7 months and <3.5 g/dl for children aged >7 months [14].

Baseline data collected were age, sex, diagnosis categorized by organ system, length of hospital stay, length of PICU stay, and receipt of ventilator support and outcome. Pediatric index of mortality 2 (PIM2) scoring system was used to assess the severity of illness at admission and to calculate the predicted death rate (PDR).

Subjects were divided into two groups according to their albumin level as hypoalbuminemia group (hypoalbuminemia subjects) and normoalbuminemic group (subjects with normal albumin level). Subjects were also grouped into two age groups for the purpose of analysis (<7 months and >7 months). Children who were discharged against medical advice were excluded from the analysis of outcome and duration of hospital stay. All the data analyses were conducted using the SPSS version 16.0. The interval data were expressed as a mean±standard deviation. The independent sample t-test and Fisher's exact test were used to compare the albumin levels with PDR and duration of hospital or PICU stay. Mortality risk was computed using Pearson's Chi-square test. Other factors influencing mortality such as age, presence of shock, and need for ventilation and Glasgow coma scale at admission was analyzed along with the PDR to determine their association with mortality through univariate and multivariate regression analysis. p value was calculated with 95% confidence interval (CI).

RESULTS

The study population included 136 subjects out of 198 subjects admitted to PICU during the study period. 62 children were excluded (Fig. 1). The mean age of the study population was 5.29±4.84 years (range: 1 month–17 years). 81 (59.6%) subjects were male and 55 (40.4%) were female with male:female ratio of 1.47, the mean serum albumin level was 3.38±0.89 g/dL. The incidence of hypoalbuminemia in our study population was 44.1%. When two age groups were compared, it was found that, 4 out of 27 subjects in the younger age group had low albumin levels whereas 56 of 109 subjects of older age group had hypoalbuminemia. Thus, the incidence of hypoalbuminemia was significantly higher in children older than 7 months (Group II). When the PDR was compared with albumin level (Table 1), it was found that the incidence of hypoalbuminemia in children with PDR >5% (75%) was higher than the incidence seen in children with PDR <1 % (25%) (p=0.004, Fisher's exact test). The mean PIM2 score in hypoalbuminemia group was 18.68 (SD 11.10) compared to 4.26 (SD 2.18) in normal albumin level group (p<0.001). This probably reflects the higher incidence of hypoalbuminemia in critically ill children.

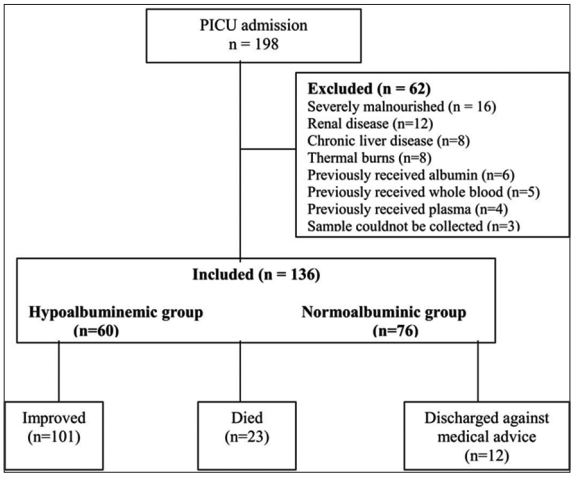

Figure 1: Temporal profile of subject admitted to pediatric intensive care unit

Table 1: Baseline demographic data of the study population

n=136	Hypoalbuminemic group n=60 (%)	Normoalbuminemic group n=76 (%)
Age groups		
Group 1 (1–7 months) n=27	4 (14.8)	23 (85.2)
Group 2 (7 months–18 years) n=109	56 (51.4)	53 (48.6)
Male: Female ratio	1.6:1	1.8:1
Mean serum albumin (g/dL)	2.64±0.28	3.72±0.28
PDR (PIM2 score)		
<1% (n=40)	10 (25)	30 (75)
1–5% (n=84)	41 (48.8)	43 (51.2)
>5% (n=12)	9 (75)	3 (25)

PDR: Predicted death rate, PIM2: Pediatric index of mortality 2

The diagnostic categories of 136 patients are mentioned in Table 2. It was observed that the incidence of hypoalbuminemia in infectious disease category was higher than other illnesses (24 out of 29). 17 out of 29 subjects in this category had sepsis (Table 3). Longer duration of PICU stay was observed in children with hypoalbuminemia compared to children with normal albumin levels, however, the difference was not statistically significant. (95% CI for difference 1.86–3.03; p=0.15, independent sample t-test). No significant statistical difference was observed between hypoalbuminemia group and normal albumin level group when considering the duration of hospital stay. (95% CI for difference 1.74–4.63; p=0.372).

The need for ventilatory support was significantly higher in children with hypoalbuminemia (30%; 18 of 60) as compared in children with normal albumin levels (9.2%; 7 of 76) (odds ratio (OR) 4.2) (p=0.003, Fisher's exact test). The mean serum albumin in mechanically ventilated children was 2.66±0.82 g/dL, compared to 3.55±0.82 g/dL in non-ventilated children (p=0.003,

Independent sample t-test). Finally, when considering the outcome, children with hypoalbuminemia had a mortality rate of 32.1% (18 of 56) which was 4.38 times greater than the normal albumin level group, i.e., 7.3% (5 of 68) (p=0.001, using Pearson Chi-square test). The mean serum albumin in expired children was 2.59±0.79 g/dL, compared to 3.54±0.82 g/dL in survivors (p=0.002, Independent sample t-test).

Univariate binary and multivariate logistic regression analyses were performed to investigate whether hypoalbuminemia at admission was independently associated with mortality (Table 4). Factors those were potentially associated with mortality such as age <1 year at admission, shock at admission, GCS <8 at admission, illness severity as assessed by the PIM2 score, and need for ventilatory support were included in the regression analyses. The majority of factors except age were significantly associated with mortality in the unadjusted binary logistic regression analysis. The association of serum albumin levels with mortality remained significant even after adjusting for age and PDR by PIM2 score (OR=3.68; 95% CI, 1.76–7.74; p<0.001).

Table 2: Diagnostic categories of albumin group

Diagnostic categories	Hypoalbuminemia group	Normoalbuminemic group
n=136	n=60 (%)	n=76 (%)
Neurological (n=41)	12 (29.2)	29 (70.8)
Infectious disease (n=29)	24 (82.8)	5 (17.2)
Respiratory (n=21)	4 (19.1)	17 (80.9)
Cardiovascular (n=12)	7 (58.3)	5 (41.7)
Oncology (n=10)	5 (50)	5 (50)
Renal (n=7)	3 (42.8)	4 (57.2)
Gastrointestinal (n=5)	2 (40)	3 (60)
Toxicology (n=8)	1 (12.5)	7 (87.5)
Others (n=3)	2 (66.6)	1 (33.4)

Thus, hypoalbuminemia was an independent predictor of mortality.

Although hypoalbuminemia was present in majority of the subjects; albumin infusion was not given to all children. As it is expensive, we used albumin only as a replacement in those children with septic shock whose serum albumin was <2 g/dL and children were hypotension persisted in spite of fluid boluses. Albumin was supplemented to only 16 of 60 subjects who had hypoalbuminemia. However, 9 of those 16 children expired (p=0.074; Pearson's Chi-square test).

DISCUSSION

Critical illness alters the distribution of albumin between the intravascular and extravascular compartments. Altered distribution is related to an increase in capillary permeability due to dysfunction of the endothelial barrier secondary to chemical mediators. Studies have shown up to 300% rise in the transcapillary escape rate of albumin in patients with the septic shock [8,9]. The rate of albumin synthesis may also be significantly altered in critical illness. The inflammatory mediators mainly interleukin-6 and tumor necrosis factor-alpha decrease the rate of transcription of albumin m-RNA and the synthesis of albumin [9]. Few studies have shown that hypoalbuminemia is a common problem in critically ill children and is associated with higher mortality and morbidity [8-12].

We found hypoalbuminemia in more than 30% of the children admitted to PICU, which is consistent with other studies. The incidence of hypoalbuminemia in studies on critically ill children ranges from 30 to 50%. In a study, Horowitz and Tai found the incidence of hypoalbuminemia to be 33% at admission to the PICU [8]. Similar to other studies, the incidence of hypoalbuminemia was more common in children with infectious disease and sepsis. Among infectious diseases, all children with

Table 3: Comparison of albumin level groups with reference to duration of PICU stay, hospital stay, mechanical ventilation and outcome

n=124	Hypoalbuminaemic (n=56)	Normoalbuminaemic (n=68)	95% CI	p
Duration of PICU stay (mean±SD days)	4.2±3.02	3.64±3.28	1.86–3.03	0.12^
Duration of hospital stay (mean±SD days)	11.8±9.76	13.78±12.67	1.74–4.63	0.37^
Recipients of ventilatory support (n=25)	18	7		0.003*
Outcome				
Died (n=23)	18	5		0.001**
Improved (n=101)	38	63		

^Independent Sample t-test; *Fisher's exact test; **Pearson's Chi-square test. PICU: Pediatric intensive care unit, CI: Confidence interval, SD: Standard devation

Table 4: Univariate and multivariate logistic regression analyses of variables potentially associated with mortality

n=124	Univariate binary logistic regression		Multivariate logistic regression	
	*OR (95% CI)	p	**AOR (95% CI)	p
Age <1 year	1.02 (0.96–1.08)	0.42	1.08 (0.96–1.18)	0.36
Presence of shock	1.18 (1.15–1.21)	<0.001	1.14 (1.10–1.18)	<0.001
GCS <8	1.36 (1.28–1.46)	<0.001	1.18 (1.12–1.24)	<0.001
Need for ventilatory support	4.13(1.58–10.81)	0.003	3.11 (1.63–5.92)	0.001
Hypoalbuminemia	5.96(2.04–17.44)	<0.001	3.68 (1.76–7.74)	<0.001
PIM2 Score	3.98(1.50–10.40)	<0.001	2.34 (0.9–6.2)	<0.001

*Odds ratio, **Adjusted odds ratio, OR: Odds ratio, CI: Confidence interval

dengue fever were hypoalbuminemia. Some studies have followed the progression of hypoalbuminemia in the critically ill during the PICU stay [9,10,15]. Durward *et al*. found that the incidence of admission hypoalbuminemia was 57%, increasing to 76% at 24 h [9]. In a study conducted by Tiwari *et al*., hypoalbuminemia at admission was 21% (92 of 435) that increased to 34% at the end of 1st week and to 37% (164 of 435) during rest of the PICU stay [10]. However, repeat serum albumin could not be estimated in all our subjects.

In contrast to other studies, we used PIM2 scoring system to assess the severity of illness at admission and to calculate the PDR [16,17]. Pediatric risk of mortality (PRISM) score was not used as comprehensive metabolic workup, and blood investigations could not be done in all of the subjects. Studies have shown that PIM 2 score compares well with the PRISM score especially, in the developing countries [18,19]. In a study conducted at Women's and Children's Hospital, University of Adelaide, PIM 2 scoring system was found to be the most accurate among PIM, PRISM, and PRISM III [19]. According to an Indian study, PIM2 2 score was found to have excellent discriminatory power in differentiating death and survival; although, it overpredicted the death rate [20].

Few studies conducted in children showed an association of hypoalbuminemia with an increased risk of mortality. In the study conducted by Tiwari *et al*., hypoalbuminemia children had higher PRISM scores (12.9 vs. 7.5, $p<0.001$) and prolonged PICU stay (13.8 vs. 6.7 days, $p<0.001$); higher likelihood of respiratory failure requiring mechanical ventilation (84.8% vs. 28.8%, $p<0.001$), prolonged ventilatory support, progression to multi-organ dysfunction syndrome (87.8% vs. 16.2%), and risk of mortality (25.6% vs.17.7%). Horowitz and Tai showed that the PRISM score (11.69 vs. 6.03; $p=0.001$) and risk of mortality score (0.166 vs. 0.038; $p=0.001$) were increased in children with hypoalbuminemia compared with the normal albumin level group.

The pathophysiology of mortality and morbidity in hypoalbuminemia can be explained by the following reasons. Albumin is the major protein contributing to 80% of the plasma colloidal oncotic pressure. Hence, whatever may be the etiology of hypoalbuminemia; the final effect will be compromised intravascular volume leading to inadequate perfusion of vital organs. In addition, to this albumin plays a key role in various homeostatic mechanisms. It serves as a plasma buffer in maintaining the pH at physiological levels. It is involved in binding and transport of various endogenous substances including hormones and drugs. Due to antioxidant property, it has a definite role in preventing free radical injury from inflammatory processes.

Study was conducted by Durward *et al*. showed admission hypoalbuminemia is common in critical illness, but is not an independent predictor of mortality, as there was no difference in the mean serum albumin concentrations between survivors and non-survivors (6.8 vs. 9.5) g/l, ($p=0.96$). According to a study conducted in adolescent children on hemodialysis by Amaral *et al*., those children with albumin >3.7g/dl had fewer deaths per 100 patient - years and fewer hospitalization per time at risk. Poisson regression showed a progressive decrease in the in-hospitalization risk as albumin level increased; however, confidence intervals were similar between albumin >3.7 g/dl and <3.7 g/dl [21].

Despite the fact that hypoalbuminemia is an independent predictor of morbidity and mortality, there is no definite evidence to support the use of albumin to treat hypoalbuminemia or hypovolemia in critically ill patients [22-24]. Some studies have used albumin as volume expander for resuscitation, whereas others have only used only to correct hypoalbuminemia. The saline versus albumin fluid evaluation study conducted in 16 ICUs in Australia and New Zealand concluded that, albumin was not superior to normal saline for intravascular-fluid resuscitation in patients in the ICU and there was no difference in the 28-day rate of death from any cause [24]. In the study by Tiwari *et al*., though albumin infusion could correct hypoalbuminemia in 54 of 72 (75%) patients, there was no difference in outcome between albumin recipients and others. In our study, a very small group of subjects (n=61) received albumin infusion. However, majority of them (9 of 16) expired. We could not repeat serum albumin in all these children. Increased mortality rate in the albumin recipients would be attributed to the higher disease severity. Thus, an insufficient number of albumin recipients is one of the limitations of our study. Although we used multivariate regression analysis to prove the association of hypoalbuminemia with mortality, we could not include biochemical parameters like blood lactate level as it was not estimated in all subjects.

CONCLUSIONS

We found that hypoalbuminemia is a common feature in children admitted to the PICU. We also found, hypoalbuminemia is a significant indicator of mortality and morbidity, which is an agreement of published data in adults and children. More studies are needed to prove whether albumin supplementation in critically ill children with hypoalbuminemia improves the outcome.

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Funding: None; Conflict of Interest: None Stated.

How to cite this article: Kumar S, Aroor S, Kini PG, Mundkur S, Moideen A. Hypoalbuminemia as a marker of adverse outcome in children admitted to pediatric intensive care unit. Indian J Child Health. 2018; 5(1):6-10.